REMARKS

Claims 1-7, 9, 11-13, 17, 19-22, 24, 26-28 and 32 are presently pending and under consideration. Claims 14-16 and 29-31 stand withdrawn from consideration as being dawn to non-elected subject matter. Claims 1 has been amended to incorporate the subject matter of claim 7, which has been canceled herein. Claims 27 and 28 have been amended to correct their dependencies. No new matter has been added. Applicants respectfully request consideration of the below remarks and respectfully submit that the application is in condition for allowance. Upon entry of the amendment claims 1-6, 9, 11-13, 17, 19-22, 26-28 and 32 will be pending and under consideration.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-7, 9, 11-13, 17, 19-22, 24, 26-28, and 32 stand rejected as allegedly failing to comply with the written description requirement. The rejection has been rendered moot with regard to claim 7, which has been canceled herein. The Office Action states that "the specification does not describe the genus of compounds that have a modified nucleotide transition moiety that does not form hydrogen bonds with the target and transitions the second region to the first region." *See* Office Action at page 3. Applicants respectfully traverse. Applicants respectfully submit that the specification as filed provides written description for the claims sufficient to show a person of ordinary skill that Applicants were in possession of the invention of claims 1-7, 9, 11-13, 17, 19-22, 24, 26-28, and 32. As described below, the specification teaches both structural and functional characteristics of the elements recited in claims 1-7, 9, 11-13, 17, 19-22, 24, 26-28, and 32.

What is required to meet the written description requirement "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). When determining whether a specification contains adequate written description, one must make an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad Pharmaceuticals, Inc. v. Eli Lilly*, 598 F.3d 1336, 1351 Fed. Cir. 2010)(*en banc*). Applicants respectfully submit that the specification as filed provides written description for the claims sufficient to show that Applicants were in possession of the invention

The specification describes structural criteria of the elements recited in the claimed methods.

The specification explains that in certain circumstances, oligonucleotides having regions differently modified nucleosides are desirable. When certain such oligonucleotides hybridize to a target RNA, they form duplexes having regions of different conformations. For example, the specification describes gapmers that hybridize to RNA resulting in duplexes having A-form helices in the wings and a B-form helix in the gap. *See* Specification at page 12. In certain such instances, it is desirable to include one or more transition moieties to reduce the conformational strain as the helix transitions from one conformation to the other. Transition moieties are "capable of modulating transfer of the helical conformation characteristic of an oligonucleotide bound to its 3'hydroxy to an oligonucleotide bound to its 5' hydroxyl, when the oligonucleotide is in a duplex with RNA." *Id.* at page 12. Thus, the transition moiety is typically placed "at the junction of the regions, so as to impart a transition between the two regions of differing conformation." *Id.*

The Specification describes structures and characteristics that impart transition between two regions of differing conformation. For example, the Background of the Invention discusses double stranded nucleic acids having different confirmations, as follows:

> Specifically, the deoxyribonucleotides within dsDNA form a southern C_2'-*endo* sugar conformation resulting in a B-form helical conformation, whereas ribonucleotides within dsRNA form a northern C_3'-*endo* pucker and an A-form helical geometry. In contrast, the deoxyribonucleotides of the RNA/DNA heteroduplex have been shown to adopt an eastern O_4'-*endo* sugar pucker resulting in a helical conformation where the RNA strand adopts A-form geometry and the DNA strand shares both the A- and B-form helical conformations.

Specification at pages 2-3. The specification also provides a large number of examples. *See for example*, pages 13-14, 40-44, 95-96, 98-109, and 110-117. Certain transition moieties are flexible and/or have geometric conformations that are in between those of the two regions they are transitioning. *See for example*, pages 95-96. The conformations of a many nucleosides are known or may be determined by one of ordinary skill. See for example, Saenger, W. (1984) *Principles of Nucleic Acid Structure*, Springer-Verlag, New York (cited at page 100 and incorporated by reference in the specification at page 117). Those conformations may be manipulated by modifying the sugar, base, and or linkage of a nucleoside, including, but not limited to, the large number of such modifications specifically provided and characterized in the

present specification. Applicants submit that the transition moieties of the present claims are described and exemplified in the specification sufficient that one of skill in the art would appreciate that the inventors were in possession of the invention as claimed.

The Examiner further contends that the specification does not provide structural criteria to determine whether a modified base will form hydrogen bonds with target RNA and whether it will stack with adjacent bases. Applicants respectfully submit that one of ordinary skill can easily make such determinations based on the structure of the modified base and principles well known in the art.

As further evidence that the genus is well characterized, Applicants respectfully draw the Examiner's attention to claims 9, 11-16, 24, and 26 -31 as they were originally filed. Each of these dependent claims recites either a more specific genus of transition moieties of the genus than claim 1, or a distinct transition moiety species. For example, claim 12 recites that "the modified base moiety is a universal base, a promiscuous base, a size expanded base, or a fluorinated base." The originally filed specification discusses each of these types of bases and their structural properties at length, for example at page 35 and at pages 38-39, and further provides citations to one or more references describing each type of base. Additionally, original claims 13 and 28, which depend indirectly from claim 1, recite tetrafluoroindolyl. Tetrafluoroindolyl has a specific chemical structure, and a skilled artisan could instantly envisage its chemical structure. Applicants respectfully request that the Examiner consider the limitations of each of the dependent claims, as they were filed originally, when assessing the specification's compliance with 35 U.S.C. § 112, first paragraph.

Finally, the Examiner asserts that the specification fails to demonstrate that a nucleoside comprising tetrafluoroindolyl acts via the mechanism of claim 11. Applicants note that claim 11 does not recite a mechanism. Rather, it describes characteristics; that the base does not form hydrogen bonds with the target RNA and that it is capable of π stacking. Applicants submit that it would have been apparent to one of skill in the art that tetrafluoroindolyl possesses these characteristics based on its structure, which appears on page 110.

In view of the above remarks, Applicants respectfully request withdrawal of the rejection of claims 1-7, 9, 11-13, 17, 19-22, 24, 26-28, and 32 for allegedly failing to comply with the written description requirement.

Rejections under 35 U.S.C. § 103

Claims 1-7, 11-13, 17, 19-22, 24, 26-28, and 32 were rejected as allegedly rendered obvious by Krotz *et al.* (US Patent Application Publication No. 2003/0096770, hereinafter "Krotz") in view of Lai *et al.* (J. Am. Chem. Soc. Vol. 126, No. 10, 2004, hereinafter "Lai"). Applicants request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 because the Office Action does not provide a reason why one of ordinary skill in the art at the time of the invention would have combined Krotz and Lai to arrive at an oligonucleotide having the claimed tetrafluoroindolyl modifications.

To establish a *prima facie* case of obviousness, it remains necessary to identify some reason that would have led a person skilled in the art to modify the teachings of a reference in a particular manner. "In cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda Chemical Indus., Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 1357 (Fed. Circ. 2007); *See also Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir2009) (holding that there must be some reason ''to select and modify a known compound''); *Ortho-McNeilPharmaceutical, Inc. v. Mylan Labs,Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). For at least the reasons set forth below, the Office Action fails establish a *prima facie* case of obviousness.

The Office Action states that Krotz teaches a method of modulating target RNA expression using phosphorothioate linked oligonucleotides that have "a first region of nucleotides of one conformation, and a second region that is 5' to the first region that comprises 2'-O-methoxyethyl groups," but that "Krotz *et al.* do not teach tetrafluoroindolyl modifications." *See* Office Action at 5. The Office Action attempts to remedy Krotz's silence towards tetrafluoroindolyl modifications with the Lai reference, stating that it "would have been obvious to incorporate fluorinated nucleotides [of Lai] into the oligonucleotide of Krotz et al…since Krotz *et al.* teach each of the claimed modifications as preferred modifications to increase the binding affinity and enhance the overall activity of the oligonucleotide." *See* Office Action at page 6.

The Office Action, however, does not provide a reason why one would incorporate the tetrafluoroindolyl modifications taught in Lai with the oligonucleotides taught by Krotz because

Lai teaches that the incorporation of fluorinated nucleosides *destabilizes* binding affinity with natural bases, e.g. RNA. For example, Lai at page 3040 states that:

> Initial experiments pairing the two fluorinated nucleosides opposite natural DNA bases in a 12-bp duplex confirmed they pair with low stability opposite hydrophilic nucleobases… However, when paired opposite themselves, a significant degree of stability was regained for both compounds.

Lai's discussion focuses on the selective fluoro-fluoro pairing preferences between short DNA strands that each have 1-2 modified fluorinated base replacements. Lai's discussion of a "new, selective base-pairing system orthogonal to the natural genetic system," refers to the selective pairing of fluorinated base analogues with each other as an alternative to Watson-Crick hydrogen bonding. *See* id. Lai does not present any data suggesting that fluorinated nucleobases increase or enhance interactions with naturally occurring RNA nucleobases. If anything, Lai teaches away from the use of fluorinated nucleobases as tools to enhance the RNA-binding affinity of an oligonucleotide. As stated above, Lai teaches that fluorinated nucleosides pair poorly opposite natural DNA, which is inapposite with the rationale stated in the Office Action for combining Krotz with Lai.

Additionally, the Office Action states that Krotz teaches that "fluorinated oligonucleotides are preferred." *See* Office Action at page 5. Krotz, however, teaches that oligonucleotides fluorinated *at the 2'-position* of the ribose are preferred. *See* Krotz, for example, at ¶¶ [0121] and [0047], stating "[o]ther preferred modifications include…2'-fluoro (2'--F)." Krotz does not teach a preference for oligonucleotides having fluoro modified nucleobases, nor does Krotz provide any reason for making such modifications.

Since the Office Action does not identify any reason why one having skill in the art would combine Krotz with Lai to arrive at an oligonucleotide having any of the claimed modifications, Applicants respectfully request withdrawal of the rejection of claims 1-7, 11-13, 17, 19-22, 24, 26-28, and 32 under 35 U.S.C. § 103.

CONCLUSION

In light of the amendments and accompanying remarks, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

Respectfully submitted,

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